The effect of botulinum toxin type a on overactive bladder symptoms in patients with multiple sclerosis: a pilot study

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Abstract: PURPOSE: Patients with multiple sclerosis often experience overactive bladder symptoms. High dose intradetrusor botulinum toxin A treatment is effective but often results in urinary retention and urinary diversion via a catheter. In this pilot study we evaluated whether only 100 U botulinum toxin A would significantly decrease overactive bladder symptoms in patients with multiple sclerosis without impairing pretreatment voluntary voiding. MATERIALS AND METHODS: Included in our study were 12 patients with multiple sclerosis who had overactive bladder symptoms such as urgency, frequency and/or urgency incontinence. The treatment effect was evaluated using data on 3 consecutive visits, that is before, and a mean +/- SD of 46.2 +/- 11.9 and 101 +/- 21 days after intradetrusor injection of 100 U Botox, including the results of cystometry and uroflowmetry at visits 1 and 2, and uroflowmetry alone at visit 3. Patients completed a 3-day voiding diary for all 3 visits. RESULTS: Maximum bladder capacity significantly increased and maximum detrusor pressure decreased. Daytime and nighttime frequency, urgency and pad use significantly decreased. Post-void residual volume significantly increased initially but decreased until 12 weeks. Median time to re-injection due to recurrent overactive bladder symptoms was 8 months. CONCLUSIONS: Overactive bladder treatment in patients with multiple sclerosis using 100 U Botox intradetrusor injections seems to be effective and safe. Despite slightly impaired detrusor contractility most patients still voided voluntarily without symptoms. Thus, 100 U Botox may be a reasonable treatment option for overactive bladder symptoms in patients with multiple sclerosis who still void voluntarily.

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THE EFFECT OF BOTULINUM TOXIN TYPE A ON OVERACTIVE BLADDER SYMPTOMS IN PATIENTS WITH MULTIPLE SCLEROSIS: A PILOT STUDY

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ABSTRACT

Purpose: Patients with MS often experience OABS. High dose BoNT/A intradetrusor treatment is effective but often results in urinary retention and urinary diversion via a catheter. In this pilot study we evaluated whether only 100 units onabotulinumtoxinA would significantly decrease OABS in patients with MS without impairing pre-treatment voluntary voiding.

Materials and Methods: Included in our study were 12 patients with MS who had OABS such as urgency, frequency and / or urgency incontinence. The treatment effect was evaluated using data on 3 consecutive visits, that is before, and a mean ± SD of 46.2 ± 11.9 and 101 ± 21 days after intradetrusor injection of 100 units Botox®, including the results of cystometry and uroflowmetry at visits 1 and 2, and uroflowmetry alone at visit 3. Patients completed a 3-day voiding diary for all 3 visits.

Results: Maximum bladder capacity significantly increased and maximum detrusor pressure decreased. Daytime and nighttime frequency, urgency and pad use significantly decreased. PVRV significantly increased initially but decreased until 12 weeks. Median time to re-injection due to recurrent overactive bladder symptoms was 8 months.

Conclusions: Overactive bladder treatment in patients with MS using 100 units OnabotulinumtoxinA intradetrusor injections seems to be effective and safe. Despite slightly impaired detrusor contractility most patients still voided voluntarily without symptoms. Thus, 100 units OnabotulinumtoxinA may be a reasonable treatment option for OABS in patients with MS who still void voluntarily.

Key words: urinary bladder; overactive bladder; multiple sclerosis; botulinum toxin A; urination disorders

INTRODUCTION

LUTD is common in patients with MS and can severely impair QoL in addition to the restrictions already experienced due to the neurological disease [1-4]. Of the patients 10% are already affected by detrusor and sphincter disorders at the initial MS diagnosis [1]. Initial symptoms of LUTD are often irritative, such as urgency and frequency, but incontinence or urinary retention also occurs often [1]. In the MS course the prevalence and severity of these symptoms inevitably increase and up to 75% of patients with MS experience bladder problems during the disease course [3-5]. A point is commonly reached at which patients with MS do not tolerate first line antimuscarinic treatment or find the effects insufficient to treat OABS and second line treatment becomes necessary [6].

BoNT/A is an effective second line treatment for OABS in neurogenic cases. Most often a dose of 300 units is chosen when using OnabotulinumtoxinA for intradetrusor injection [7]. However, patients with MS often present with initial PVRV and treating them with 300 units OnabotulinumtoxinA may probably result in high PVRV or urinary retention, requiring ISC or an indwelling catheter [1, 6-8]. This is often not satisfactory in patients with MS who are still ambulatory and voluntarily empty most of the bladder capacity.

Recently 100 units OnabotulinumtoxinA were noted to effectively alleviate OABS in non-neurogenic cases without causing urinary retention or a significant increase in PVRV [9, 10]. To our knowledge there is as yet no proof that 300 units OnabotulinumtoxinA are needed to efficiently treat OABS in MS cases. Drug treatment usually starts with a low dose that can be increased as needed, rather than with a high dose.

The aims of our study were to (1) investigate whether intradetrusor injections of only 100 units OnabotulinumtoxinA would sufficiently treat OABS in patients with MS and 2) observe whether 100 units OnabotulinumtoxinA would prevent urinary retention and, thus, provide the possibility of avoiding or decreasing the frequency of de novo ISC. We hypothesized that 100 units OnabotulinumtoxinA would alleviate OABS in our MS population but efficient, symptom-free voluntary voiding would still be possible.

MATERIALS AND METHODS

After receiving approval from the local ethics committee we recruited patients with MS who consulted our neuro-urology department for treatment of LUTS. Study inclusion criteria were a proven diagnosis of MS; OABS with or without incontinence, as documented by 3-day voiding diary, with at least 3 urgency episodes in 3 days that were refractory to at least 2 antimuscarinic agents, each ingested for 1 month; treatment naïve status to BoNT/A before the first consultation at our department; preserved voluntary voiding or voluntary voiding as the only way of bladder emptying; ability and willingness to perform ISC; and written informed consent. Study exclusion criteria were neurological diseases other than MS, MS relapse 6 months before or during the evaluation period, previous LUT surgery or malignancy and previous BoNT/A treatment.

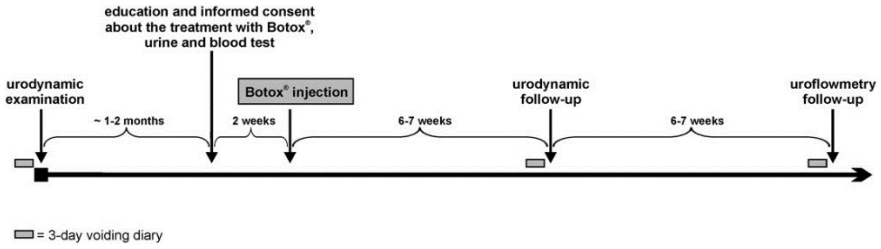

Figure 1 Study course

All patients had to complete 5 visits, including initial urodynamic evaluation at visit 1, blood and urine test before BoNT/A intradetrusor injection at visit 2, Botox® intradetrusor injection at visit 3, post-treatment urodynamic evaluation 6 to 7 weeks after injection at visit 4 and uroflowmetry follow-up 12 to 14 weeks after injection at visit 5 (**Figure 1**). At visits 1, 4 and 5 a 3-day voiding diary was completed (**Figure 1**).

BoNT/A intradetrusor injection at visit 3 was done with a 19Fr or 22Fr rigid cystoscope and a 22 gauge 0.7 mm needle 8 mm long. Only half of the needle was inserted. Each patient received 100 units OnabotulinumtoxinA diluted in 10 ml 0.9% saline and distributed over 10 injection sites at 1 ml each. Local anesthesia of the bladder mucosa was achieved with 50 ml 2% lidocaine / 8.4% bicarbonate solution instilled into the bladder for 10 minutes before injection.

Evaluated outcome parameters were maximum detrusor pressure ($pDet_{max}$), maximum cystometric capacity (MCC), bladder volume at first desire to void (FDV) on video cystometry at visits 1 and 4; voided volume, maximum flow rate (Q_{max}), PVRV on uroflowmetry at visits 1, 4 and 5; daytime and nighttime frequency, incontinence episodes, urgency episodes and number of pads used on voiding diary at visits 1, 4 and 5. All outcome parameters were defined according to the International Continence Society standardization of terminology [11].

We also assessed the extended disability symptom scale (EDSS) in all patients to provide information on individual impairment (**Table 1**) [12]. The EDSS range is 0.0—normal neurological examination to 10.0—death from MS and it quantifies the disability in 8 functional systems. Procedure pain and patient satisfaction were evaluated using 2 visual analogue scales (VAS) with a range of 1—no pain or complete dissatisfaction to 10—worst pain or maximum satisfaction.

Patients were eligible for re-injection on demand but not before 3 months after the previous injection. The reinjection appointment was scheduled by patients when OABS recurred.

Video cystometry outcome parameters were statistically compared between visits 1 and 4 using the nonparametric Wilcoxon signed ranks test with $\alpha = 0.05$. Uroflowmetry and voiding diary outcome parameters were statistically compared among visits 1, 4 and 5 using the nonparametric Wilcoxon signed ranks test but due to multiple comparisons $\alpha = 0.025$.

Table 1 Patient demographics

Patient No. - Gender	Age [years] at BoNT/A injection	Age [years] at MS diagnosis	EDSS
1 - F	43	35	3.0
2 - F	58	41	3.0
3 - F	60	45	4.5
4 - F	39	27	5.5
5 - F	50	20	6.0
6 - F	62	29	6.0
7 - F	51	34	7.5
8 - M	50	33	6.0
9 - F	43	37	4.5
10 - F	65	35	3.0
11 - F	59	52	6.0
12 - F	38	21	4.5
Mean ±SD	51.5 ±9.3	34.1 ±9.3	5.0 ±1.5

BoNT/A botulinum neurotoxin A, EDSS extended disability symptom scale, MS multiple sclerosis

RESULTS

One man and 11 women with a mean ± SD age of 50.7 ± 10 years met all study inclusion and exclusion criteria, and were evaluated (**Table 1**). Mean time between visits 3 and 4 was 44.1 ± 10.6 days and between visits 3 and 5 it was 113.8 ± 61.4 days. Before visit 2 no patient performed ISC.

All patients showed OABS on 3-day voiding diary at visit 1, although some had normal video cystometry results. No patient had VUR before or after treatment. DO with incontinence was observed on cystometry in 7 patients before and in 3 after Botox® application.

Mean MCC significantly increased in 9 patients from 352.6 ml at visit 1 to 538.8 ml at visit 4 ($p = 0.008$). The remaining 3 patients already had an initial MCC of about 600 ml. However, comparison of all 12 MCCs between visits 1 and 4 revealed a significant increase ($p = 0.034$, **Figure 2**). Mean volume at FDV increased significantly from 340.3 ± 233 ml at visit 1 to 453.1 ± 200 ml at visit 4 ($p = 0.05$). In all patients $Pdet_{max}$ decreased significantly from a mean of 38.0 cmH_2O at visit 1 to 16.3 cmH_2O at visit 4 ($p = 0.004$, **Figure 3*A***).

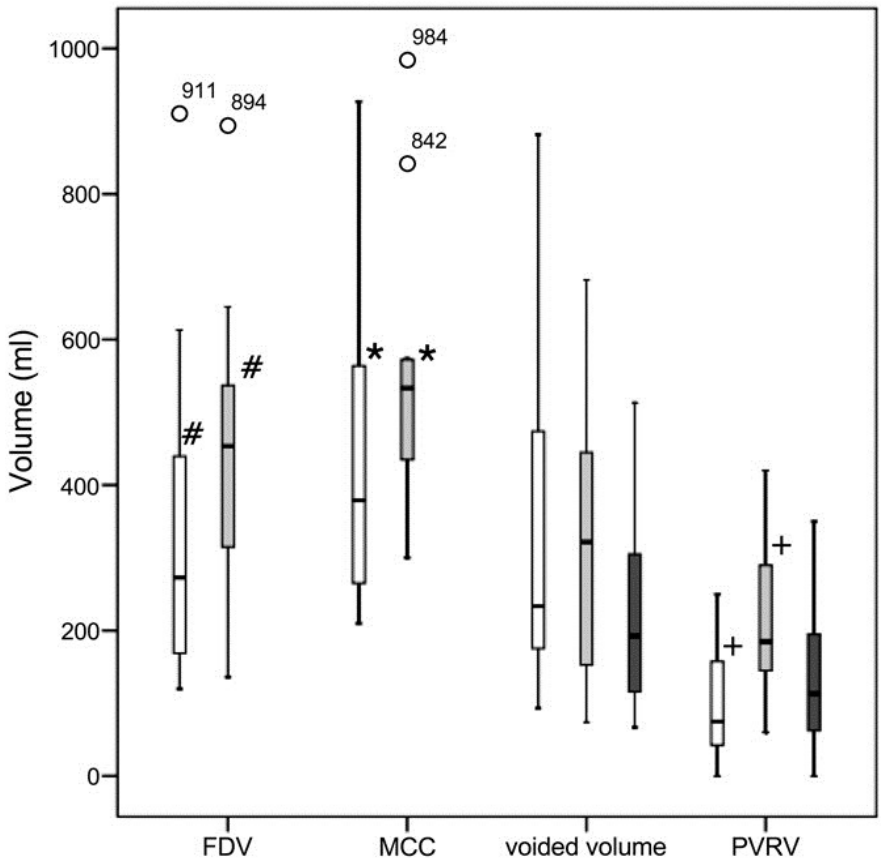

Figure 2 Volume at FDV and MCC at visits 1 (open bars) and 4 (light gray bars), and voided volume and PVRV at visits 1, 4 and 5 (dark gray bars) in all patients. Box plots indicate minimum, 25% percentile, median, 75% percentile and maximum. Pound sign indicates p = 0.05. Asterisk indicates p = 0.034. Plus sign indicates p = 0.003.

Voiding diary data showed a significant decrease in frequency, urgency episodes and pad use from visits 1 to 4 (**Table 2, Figure 4**). This significant decrease was sustained up to visit 5 (**Table 2, Figure 4**). We noted a significant decrease in nocturia from visits 1 to 4 (**Table 2, Figure 4**). However, this significant decrease was not sustained up to visit 5, although mean nighttime frequency was still lower at visit 5 than at visit 1 (**Table 2**). The mean number of incontinence episodes decreased continuously from visits 1 to 5 but we noted no significant difference between visits in the number of incontinence episodes (**Table 2, Figure 4**).

We found no significant differences between visits in voided volume and Q_{max}, although each parameter seem to slightly decrease from visits 1 to 5 (**Table 2**, **Figure 2**, and **Figure 3*B***). PVRV significantly increased from visits 1 to 4 (**Table 2**, **Figure 2**). However, until visit 5 PVRV decreased back toward baseline values and we noted no significant difference between visits 1 and 5 (**Table 2**, **Figure 2**).

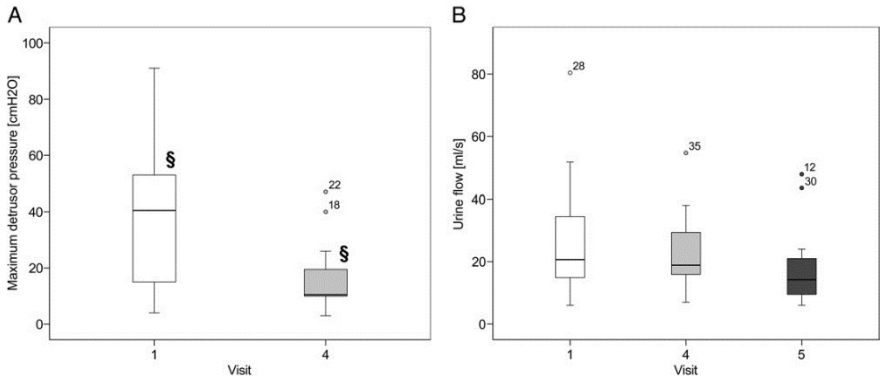

Figure 3 *A*, Pdet max during filling cystometry in all patients at visits 1 and 4. *B*, Qmax during uroflowmetry in all patients at visits 1, 4 and 5. *ml/s*, ml per second. Box plots indicate minimum, 25% percentile, median, 75% percentile and maximum. § indicates p = 0.004

After visit 3 ISC was needed only in 2 patients once to twice daily on demand. One patient needed a suprapubic catheter. The need for ISC was based on symptoms, eg persistent OABS or recurrent UTI, and not related to a certain PVRV. The mean incidence of symptomatic UTI was 1.0 ± 1.1 at 12 months before BoNT/A injection and 1.1 ± 1.4 between BoNT/A injection and re-injection. Other adverse events were mild self-limited hematuria in 6 patients and mild self-limited injection site pain in 8. The mean VAS pain score in those cases was 2.8 ± 1.9 points.

The mean VAS satisfaction score in all patients was 7.3 ± 2.1. Ten of 12 patients agreed to be treated with BoNT/A again. Of those 10 patients 1 was lost to further follow-up and 9 required re-injection after a mean of 11 ± 6.1 months (median 8, range 5 to 22). The 2 patients who did not agree to re-injection were not satisfied with the treatment outcome, although 1 showed significant improvement in the urodynamic and voiding diary parameters.

Table 2 Three-day voiding diary and uroflowmetry results in 12 patients at visits 1, 4, and 5.

		Visit 1 [mean ±SD]	Visit 4 [mean ±SD]	p Value vs Visit 1*	Visit 5 [mean ±SD]	p Value vs Visit 1*
No. voids	Daytime	11.4 ±3.5	7.1 ±2.1	p = 0.002	8.5 ±2.6	p = 0.004
	Nighttime	2.4 ±1.4	1.3 ±1.2	p = 0.005	1.9 ±2.0	p = 0.107
No. episodes / day	Inconti-nence	3.8 ±5.1	1.9 ±3.2	p = 0.041	1.0 ±1.4	p = 0.214
	Urgency	9.1 ±5.7	2.8 ±3.8	p = 0.013	4.4 ±5.2	p = 0.008
No. pads / day		1.9 ±09	0.8 ±0.8	p = 0.020	0.7 ±0.9	p = 0.011
Uroflow-metry	Voided vol. (mL)	337.4 ±256.5	330.8 ±186.2	p = 0.875	221.3 ±132.4	p = 0.239
	Qmax (mL/s)	27.9 ±21.0	23.1 ±13.2	p = 0.530	18.7 ±13.5	p = 0.055
	PVRV (mL)	98.3 ±77.6	222.1 ±113.2	p = 0.003	135.2 ±94.8	p = 0.328

PVRV post void residual volume, *α = 0.025

DISCUSSION

Our study showed significant improvement in all cystometric and voiding diary parameters except incontinence episodes after intradetrusor injection of only 100 units OnabotulinumtoxinA. Currently only 2 studies are available of the effect of BoNT/A intradetrusor injections in a pure MS population and each describes the effect of 300 units [6, 13]. Direct comparison of the studies by Schulte-Baukloh [13] and Kalsi [6] with our study remains difficult and no direct conclusion can be drawn about which dose is more effective. However, somewhat similar results were observed in cystometric parameters at 4 to 6-week follow-up, and for voiding diaries at 4 to 6 and 12 to 16-week follow-up. Nevertheless, decreased daytime and nighttime frequency, incontinence and urgency appear more pronounced and persistent in the study by Kalsi [6] than in our series. Moreover, in our study the mean number of urgency episodes, and mean daytime and nighttime frequency showed a tendency to increase again after 12-week follow-up, although urgency episodes and daytime frequency remained significantly decreased compared to before treatment. Our follow-up was only until 12 weeks after treatment and the median interval after which patients requested re-injection was 8 months. This shows that from the patient viewpoint the effect of 100 units OnabotulinumtoxinA lasted for a period comparable to that in the study by Kalsi [6].

Our results show that intradetrusor injections of 100 units OnabotulinumtoxinA alleviated OABS significantly in our MS population. However, 100 units OnabotulinumtoxinA do not preserve initial detrusor contractility and cannot generally prevent the need for de novo ISC or even urinary diversion via a catheter. PVRV increased significantly, and mean Q_{max} and voided volume decreased, although not significantly. BoNT/A intradetrusor injections may most often cause a higher incidence of de novo ISC and increased PVRV in patients with neurogenic OABS but not or only rarely in those with NNOAB presumably due to the already neurologically compromised process of bladder emptying, e.g. DSD, in the neurogenic OABS population [6]. However, that observation may be biased or influenced by the use or omission of a certain PVRV threshold at which to start ISC as well as the potential difference of those thresholds among studies. A recent study using 200 units OnabotulinumtoxinA in patients with NNOAB showed quite a high number with de novo ISC with a PVRV threshold requiring ISC at 200 ml regardless of symptoms [14]. Thus, using or not using a PVRV threshold for ISC and its level can significantly influence the study outcome. In our series we did not use a fixed PVRV threshold for ISC but rather focused on symptomatology.

To our knowledge there is yet no evidence-based consensus of PVRV threshold use, although experts on this topic from the United Kingdom seems to be ahead [15]. The suggested United Kingdom consensus of a 100 ml PVRV cutoff for ISC regardless of symptoms is straightforward and seems to be reasonable treatment since full functional bladder capacity is available in the storage phase due to complete bladder emptying by ISC [15]. Also, all patients in whom BoNT/A intradetrusor treatment is planned should be encouraged to learn ISC since increased PVRV or even urinary retention are known risk factors [7, 14, 16]. However, ISC done at least 4 to 6 times daily only because of a certain PVRV is not evidence-based and can be discussed critically. Moreover, it may not meet the individual expectations and needs of a patient with OAB.

In regard to this issue daily practice may legitimately differ from the protocol in prospective studies. To our knowledge no current study provides enough evidence to establish a certain PVRV threshold. A recent literature review stated that PVRV greater than 300 ml may be considered to favor UTI development [1]. Another group noted in a series of patients with stroke that PVRV greater than 150 ml seems to be an independent risk factor for UTI [17]. None of our patients had PVRV greater than 200 ml at 12-week follow-up or an increased incidence of UTI. Only 1 patient, who was 1 of the 2 requiring ISC twice daily, had a PVRV of 350 ml.

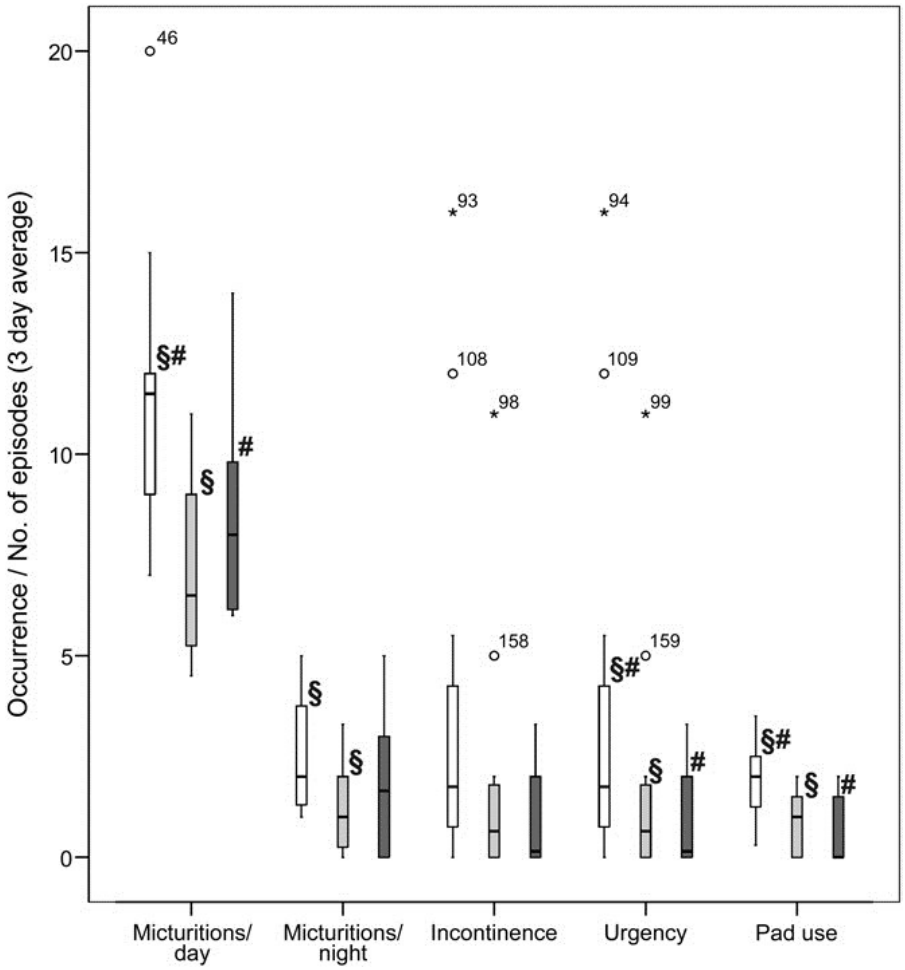

Figure 4 Three-day VD results in all patients at visits 1 (open bars), 4 (light gray bars) and 5 (dark gray bars) regarding daytime (§ indicates p = 0.002 and # indicates p = 0.004) and nighttime (§ indicates p = 0.005) frequency, incontinence, urgency (§ indicates p = 0.013 and # indicates p = 0.008) and pad use (§ indicates p = 0.02 and # indicates p = 0.011). Box plots indicate minimum, 25% percentile, median, 75% percentile and maximum of 3-day averages.

When OABS are satisfactorily treated, no recurrent UTI develops, no VUR is present and patients can still sufficiently empty the bladder without symptoms, it may be justified to omit or decrease the frequency of ISC. However, regular follow-up investigations remain mandatory since the consequences of sustained high PVRV on the UUT in this population have not yet been specifically assessed. In this context α-receptor-antagonists may be an option to decrease outflow resistance and,

thus, PVRV in these patients. In our study 100 units OnabotulinumtoxinA intradetrusor injections enabled most patients to omit or at least decrease ISC to a minimum without symptoms.

Since OABS development and severity can be quite heterogeneous in the MS population [1], a more rational approach would be to first start at a low dose and increase the dose during the treatment course according to symptoms and the treatment effect, as it is usually done with most other forms of drug therapy.

Potential limitations of this study are 1) our small number of patients, which is probably the cause of the high SD in some outcome parameters and the subsequent lack of significance, e.g. incontinence episodes, and 2) uroflowmetry and voiding diary follow-up was only up to 12 weeks, limiting information on the real duration of efficacy. Nevertheless, our pilot study presents promising first results of a different approach to OABS treatment in patients with MS and BoNT/A use in this context.

CONCLUSIONS

100 units OnabotulinumtoxinA seemed to be effective and safe for OABS in our MS study group due to significantly decreased urgency episodes, daytime and nighttime frequency, pad use and $Pdet_{max}$, and significantly increased MCC. However, initial detrusor contractility was not maintained since PVRV increased significantly and Q_{max} decreased. Nevertheless, most patients were able to remain on voluntary voiding without symptoms. The median time to when patients requested re-injection due to OABS relapse was 8 months. Results favour a treatment approach starting with a low BoNT/A dose with the possibility of increasing the dose, when applicable. This may be a reasonable OABS treatment in patients with MS who still void voluntarily.

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